

A Review: Hemodynamic Response to Carbon Monoxide

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Historically, and at present, carbon monoxide is a major gaseous poison responsible for widespread morbidity and mortality. From threshold to maximal nonlethal levels, a variety of cardiovascular changes occur, both immediately and in the long term, whose homeostatic function it is to renormalize tissue oxygen delivery. However, notwithstanding numerous studies over the past century, the literature remains equivocal regarding the hemodynamic responses in animals and humans, although CO hypoxia is clearly different in several respects from hypoxic hypoxia. Factors complicating interpretation of experimental findings include species, CO dose level and rate, route of CO delivery, duration, level of exertion, state of consciousness, and anesthetic agent used. For example, tachycardia is commonly observed, although bradycardia also can result from myocardial and/or central nervous system (CNS) hypoxemia at high carboxyhemoglobin (COHb) saturations, as can electrocardiographic abnormalities. Augmented cardiac output usually observed with moderate COHb may be compromised in more severe poisoning for the same reasons, such that regional or global ischemia result. The hypotension usually seen in most animal studies is thought to be a primary cause of CNS damage resulting from acute CO poisoning, yet the exact mechanism(s) remains unproven in both animals and humans, as does the way in which CO produces hypotension. This review briefly summarizes the literature relevant to the short- and long-term hemodynamic responses reported in animals and humans. It concludes by presenting an overview using data from a single species in which the most complete work has been done to date.

Introduction

The lethal constituent of the fumes of burning fossil fuels was not identified as carbon monoxide (CO) until the beginning of the 19th century (1). Claude Bernard (2) and John Scott Haldane (3) were among the first to investigate the cardiorespiratory and psychological effects of CO. The recent book by Pankow (4) broadly reviews the toxicology of CO, and articles by Ginsberg (5), Turino (6), and McGrath (7) have discussed limited areas of its action.

Forbes et al. (8) demonstrated the dependence of carboxyhemoglobin (COHb) saturation on ventilation rate, inhalation time, and percentage of inspired CO. More recently, Peterson and Stewart (9) and Joumard et al. (10) presented refinements in predicting COHb levels in humans, while Tyuma et al. (11) have done the same for several animal species. In general, CO uptake to an equilibrium COHb saturation is slow in large species such as humans and requires 8 to 24 hr; only 1 to 2 hr are necessary in small species such as rats (12).

Hemodynamic changes permit a rapid response to depressed blood oxygen carrying capacity; however, the hemodynamics may be altered during sustained challenge. This review summarizes such responses to CO derived from human and animal experiments. As far as

the author is aware, this is the first time this aspect of CO toxicity has been summarized in depth.

Studying the responses of a system to a challenge in isolation from one another may result in failure to appreciate interactions among the responses. Bearing this limitation in mind, the various cardiovascular parameters will nonetheless be considered one at a time in order to compare and contrast how they are influenced by CO. Acute studies are considered first, then chronic; animal studies precede human, and where possible, data from the awake state follow those obtained under anesthesia. A brief summary and integration of responses concludes each of the sections. This seems a manageable way in which to proceed considering the nonuniformity of experimental approaches in the literature, with respect to species, CO dose level, CO dose rate, route of CO delivery, study duration, rest or exercise, state of consciousness, and anesthetic agent used. Because pulse or heart rate (HR) is labile, easily measured, and has been examined in so many studies, it is discussed first.

Heart Rate

Acute

Anesthetized Animals. In 1921, Haggard (13) observed increases in heart rate (HR) with COHb between 16 and 20% in dogs; Chiodi (14) reported that HR increased sharply in dogs as COHb approached 50%. Kil-

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lick (15), however, found little change in HR until COHb reached 25 to 30%, after which it increased approximately in proportion to COHb. Marked tachycardia was noted by Einzig et al. (16) at COHb saturations between 26.5 and 41.6% in dogs, declining as CO disappeared. Ayres et al. (17) reported modest tachycardia in dogs inhaling CO, while Lillehei et al. (18) saw a rise in HR over 30 min in nembutalized dogs. Dogs were found to be more resistant to carboxyhemoglobinemia than humans by the Ayres group (17), responding with increased HR only at higher COHb.

Using chloralose-urethan anesthetized rats, Kanten et al. (19) saw modest increases in HR at 7 to 40% COHb. However, tachycardia was more prominent in the conscious state in this study, especially during the first few hours of carboxyhemoglobinemia. On the other hand, even at high COHb (40%), HR was variable in nembutalized rats (20) and anesthetized paralyzed dogs (21). King et al. (22) saw no change in HR at 50 to 65% COHb, but it is significant that the control dogs had HRs of 186 and 196 bpm because of the anesthetic (i.e., pentobarbital).

Anesthesia-induced tachycardia was also present in the study of Gutierrez et al. (23), but 50% COHb provoked some further increase in HR. According to Norman et al. (24), HR did not vary in a consistent manner with COHb saturation over the range 0 to 70% in lightly anesthetized dogs inhaling coal gas. Progressive sinus bradycardia and eventual cardiac standstill which was correctable by pacemaker were seen by Dergal et al. (25) in anesthetized dogs inhaling 2 to 10% CO.

Pindok et al. (26) saw increased HR in anesthetized dogs inhaling smoke containing 1.6% CO generated by burning charcoal and sawdust. While COHb reached 72% after 8 min, the smoke constituents produced hypoxic hypoxia and hypercapnia as well as CO hypoxia.

Conscious Animals. HR was seen to increase several fold by Santiago and Edelman (27) in goats as COHb approached 60%. Adams et al. (28) reported a 4% increase in HR in dogs at 4% COHb, with HR increasing by 20% at 20% COHb. In dogs attaining 10, 20, and 30% COHb by brief CO inhalation, Cramlet et al. (29) saw 17.6, 35.7, and 55.7% increases in HR, respectively; while in another study (30), HR rose 18% in awake dogs briefly attaining 30% COHb. Tachycardia was also noted in both conscious and de-efferented rabbits inhaling 0.2% CO (31,32).

Petajan and his colleagues (33) found that at very high COHb (65–70%), HR was severely depressed in conscious rats inhaling 1500 ppm CO for 80 min, although HR rose transiently upon initial exposure.

Adams et al. (28) found that HR did not increase during exposure to CO following administration of propranolol and suggested that tachycardia is a β -adrenergic response mediated through the sympathetic nervous system. According to Ayres et al. (34), low to moderate CO levels in resting subjects may not initiate increased sympathetic activity. It is unclear, however, whether the transient catecholamine release that occurs with carboxyhemoglobinemia (21,35,36) contributes to

cardiac speeding. In hemoglobin-free rabbits transfused with perfluorochemical emulsions, even 5, 10, and 20% CO in the inspired gas mixture fails to alter HR (37), which rules out a direct chronotropic effect of CO.

Humans. Chiodi (14) reported that HR increased sharply in men as COHb approached 50%. Sinus tachycardia, T-wave abnormalities, and other electrocardiographic changes were seen by Cosby and Bergeron (38) in patients with CO poisoning, but blood levels were not given. While Stewart et al. (39) established a direct correlation between COHb saturation and cardiac output in the range 0 to 15% in healthy humans, no change in HR was seen.

Nielsen (40), examining the effects of CO on human thermoregulation, observed HR increases at 25 to 33% COHb. Lazarev (41) has also noted cardiac acceleration both in cases of acute and chronic CO exposure in humans.

In contrast, Shephard (42) reported no change in HR in humans during 30 min of laboratory work at 2.4 to 5.4% COHb. Vogel and Gleser (43) also failed to see tachycardia in resting humans at 18 to 20% COHb, although HR at several submaximal exercise levels was greater than when not breathing CO. This was confirmed in a second study by the same group (44) and closely resembled the responses to hypoxic hypoxia. During moderate exercise in humans at 15% COHb, Pirnay et al. (45) found HR was 11.4% higher than normal. In two groups of men, one inhaling 50 ppm CO and another 100 ppm CO and working at 35% of maximal oxygen consumption rate, HR was higher than in air controls similarly working (46). Strangely, Chevalier et al. (47) found HR was lower in nonsmoking men at rest who inhaled CO after 2 and 5 min of exercise and 3 min following exercise.

Chronic

Animals. Asmussen and Vinther-Paulsen (48) found that heart rate in the dog was double control values during 10 days at 46% COHb. When CO exposure is prolonged beyond a few days or weeks, compensatory processes such as polycythemia, hypervolemia, and cardiomegaly may supervene depending upon COHb level, which alter the subsequent hemodynamic picture (Fig. 1). Significant increases in hemoglobin concentration have been observed in chronic studies (49–52). HR was unchanged in conscious goats maintained at 20% COHb for 2 weeks, although there was significant bradycardia postexposure (52). During 8 months at 11.2% COHb, no change in HR was noted in Cynomolgus monkeys (53). Likewise, in rats and mice exposed to 50 ppm CO for 650 days, no change in HR was noted based on ECG tracings (54). In dogs gradually acclimated to inhaling 1000 ppm CO for 6 to 8 hr each day for a year, HR was found to be lower (18). Similarly, HR was slightly depressed in rabbits exposed to 100 ppm CO for 2500 hr (55).

Humans. Klausen et al. (56) found no significant change in HR over 8 days in men resting at 12.5%

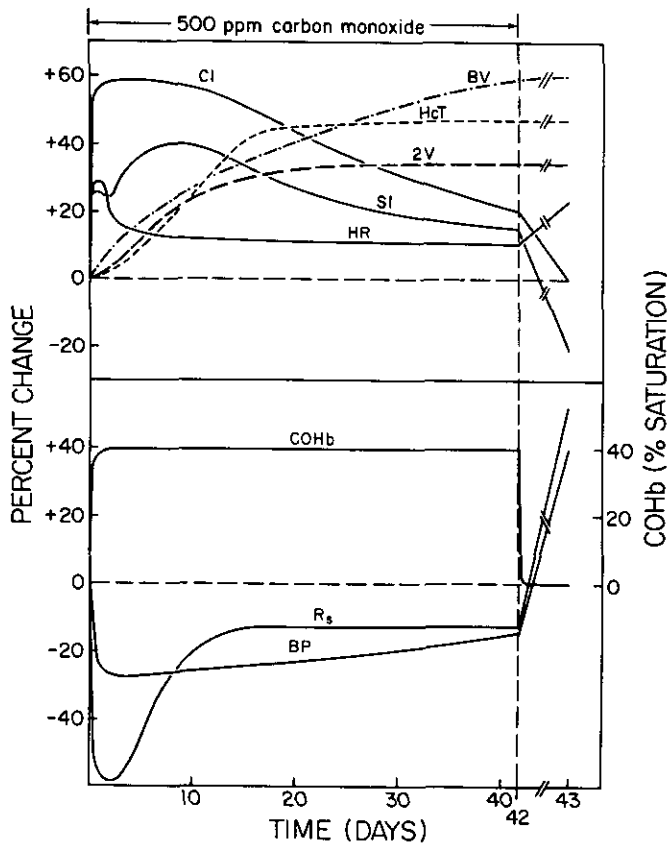


FIGURE 1. Changes in blood volume (BV), hematocrit (Hct), heart weight (2V), cardiac index (CI), stroke index (SI), heart rate (HR), carboxyhemoglobin saturation (COHb), systemic peripheral resistance (R_s), and arterial systolic blood pressure (BP) during 6 weeks' inhalation of 500 ppm carbon monoxide in the rat.

COHb. When the same men worked, HR rose relative to working men not breathing CO, in a fashion similar to acute studies. Again, this points out the limitations of examining hemodynamic responses to CO only in the resting state.

Mechanism of CO Toxicity. Since the last century, the question has remained whether binding to hemoglobin and subsequent compromise of blood oxygen carrying capacity constitutes CO's real mechanism of toxicity. In the 1940s, Drabkin et al. (57) noted that 75% COHb acutely produced in dogs by blood replacement results in none of the characteristic signs of anoxia (e.g., myocardial and cerebral necrosis) seen in dogs which inhale CO to that level of saturation. Similar experiments with like results were repeated by Ramirez et al. (58) and Goldbaum et al. (59). These investigators maintain (a) that it is the CO dissolved in the plasma that results in its toxic effects, not that attached to hemoglobin, and (b) that diffusion of CO to the cells causes its primary toxic action, possibly by binding to cytochrome oxidase, myoglobin, etc. In their view, shed blood reacted with CO and reinfused loses its dissolved CO on one transit of the lungs and is thus much less toxic than when CO is inspired, which results in higher levels of dissolved CO. Intraperitoneal uptake of 100%

CO by dogs is also claimed to be nontoxic by these investigators (61), for the same reasons. Others (62) failed to see changes in HR in rats given CO by IP injection. Coburn (60), among others, has criticized these experiments based on the mode of CO inhalation used for comparison, namely anesthetized dogs breathing 13% CO: To wit, such a high concentration of CO would be expected to saturate blood leaving the lung, resulting in lethal neurologic and myocardial sequelae, which, however, do not occur if uptake to the same final COHb saturation is achieved by inhalation of lower CO concentrations over longer time intervals.

On the other hand, IP injection of CO into dogs by Wilks (63) increased HR slightly, and Kantén and his collaborators (19) found the same degree of tachycardia following CO injection that occurs with equivalent COHb saturation produced by inhalation. Likewise, in dogs either ventilated or injected with CO, the same cardiovascular responses were recorded (23). Finally, Halebian et al. (64) found no difference in whole body oxygen consumption in dogs ventilated with either CO or N_2 and that reached the same arterial oxyhemoglobin saturation, suggesting CO was not significantly inhibiting mitochondrial oxidative metabolism. Although the evidence that CO toxicity results from binding to hemoglobin is somewhat indirect, including the known effects of CO on oxygen carrying capacity and the oxyhemoglobin dissociation curve and demonstration of small decreases in tissue P_{O_2} resulting from increases in blood COHb, the evidence for major direct effects of CO at the tissue level is equivocal, and the burden of proof remains with those who propose it.

Stroke Volume

As the codeterminant of cardiac output with HR, stroke volume (SV) or stroke index (SI) have not been seen to consistently increase in response to CO in the few studies in which it has been measured. Sylvester and his colleagues (21) reported an increase over 15 to 20 min in anesthetized paralyzed dogs under constant ventilation. King et al. (22) also saw substantial increases in SV in anesthetized dogs at 50 to 65% COHb. In anesthetized dogs receiving CO by IP injection (COHb > 50%), SV increased more than 40% (23).

SI was increased sharply under pentobarbital anesthesia in rats that had been maintained at 38 to 42% COHb for 6 weeks by CO inhalation (20). SV also increased steadily in anesthetized rats studied over 48 hr in which COHb was raised from 7 to 38% (19).

On the other hand, Cramlet et al. (29) found no change in SV in conscious dogs at 10, 20, and 30% COHb. Likewise, SV was unchanged in conscious goats maintained at 20% COHb for 2 weeks (52). However, Asmussen and Vinther-Paulsen (48) found that SV fell substantially in awake dogs at COHb values as high as 46% during 10 days.

In humans, SV was noted to increase directly as COHb increased from 0 to 15% (39). In contrast, Vogel and Gleser (43) found no change in SV in humans with

18 to 20% COHb, at rest, and even at three levels of bicycle exercise. In resting men at 12.5% COHb for 8 days, SV was unchanged (56), however, when the same men worked, SV fell relative to men working but not breathing CO.

In a chronic study, Dhindsa and Ochsner (53) reported no change in SV in *Cynomolgus* monkeys maintained at 11.2% COHb for 8 months.

Thus, SV may or may not increase in resting dogs, goats, monkeys, and humans at low to moderate COHb saturation, but sharply increases in rats at substantial COHb levels. What occurs is probably related to changes in peripheral resistance (i.e., afterload) and venous return (i.e., preload), and whether HR changes, such that total flow is commensurate with adequate tissue oxygen delivery. During exercise or at high COHb saturation, SV falls in dogs and humans, probably due to myocardial hypoxemia.

Cardiac Output

Acute

In rats monitored under chloralose-urethan anesthesia, cardiac output (Q) was observed to increase almost directly with increasing COHb saturation from 7 to 38% over 48 hr (19). Sylvester et al. (21) also reported an increase in Q over a 15- to 20-min period in anesthetized paralyzed dogs inhaling CO. Ayres and his group (17), however, saw only small initial increases in Q in dogs inhaling CO.

More recently, Gutierrez et al. (23) reported large (35–50%) increases in Q in anesthetized dogs given CO by inhalation or IP injection. Comparable and even greater increases in Q were found by King et al. (66) and King et al. (22), respectively, using similar dog preparations in which COHb reached above 50%. Using surgically denervated dogs, they showed that aortic chemoreceptor input is not necessary for this increase in Q, nor for the diversion of this increased flow to nonmuscle tissues (66).

Chiodi and co-workers (14) found no more than slight increases in Q in conscious dogs as COHb ranged up to 30%, while Q increased by as much as half at COHb near 50%. No change in Q occurred in conscious dogs brought to 10, 20, and 30% COHb within 30 min (29).

Using human subjects, Asmussen and Chiodi (67) found only a slight increase in Q at COHb up to 33%; however, in other conscious human studies, Chiodi et al. (14) reported sharp increases in Q as COHb reached as high as 48%. In patients briefly exposed to 5% CO in air, Ayres et al. (34) found 10% increases in Q, while Stewart et al. (39) established the aforementioned direct correlation between COHb and Q in humans over the range 0 to 15% COHb.

On the other hand, Ayres and his group in an early study (68) found no change in Q in humans with 4.95 to 9.69% COHb. Similarly, Vogel and Gleser (43) saw no change in Q in resting humans at 18 to 20% COHb. However, they did find Q was greater at equal levels of submaximal exercise than in air controls.

Chronic

Regarding long-term CO exposure, Penney et al. (20) observed that Q increased sharply upon initial CO exposure and remained elevated for 42 days in rats examined under anesthesia where COHb was 38 to 42%. On the other hand, Asmussen and Vinther-Paulsen (48) saw at maximum, a 15.8% increase in Q in conscious dogs during 10 days at COHb as high as 46%. Moreover, at 20% COHb, cardiac index was unchanged in conscious goats over a period of 2 weeks (52). Finally, Dhindsa and Ochsner (53) saw no change in Q or cardiac index in *Cynomolgus* monkeys maintained at 11.2% COHb for 8 months.

In men at rest who were maintained at an average of 12.5% COHb for 8 days, Q did not change (56). When the men worked, this parameter remained steady or fell relative to working men not breathing CO.

With a few exceptions (58,59,61), most investigators agree that CO exerts its morbid effect by reversibly binding with hemoglobin and decreasing oxygen-carrying capacity. It also increases the affinity of the remaining hemoglobin sites for oxygen, thus holding oxygen more tenaciously. Both phenomena contribute to tissue hypoxemia unless offset by increased tissue perfusion. Augmented Q, when it occurs, may be accomplished by increased HR, increased SV, or both. In general, Q usually increases above 20% COHb unless there is excessive myocardial hypoxemia and at lower COHb levels with physical exercise; however, the manner in which it occurs is variable; in some species or situations it involves tachycardia to a greater degree than SV, and vice versa.

Blood Pressure

Acute

Anesthetized Animals. Early on several investigators noted the lowering of blood pressure (BP) during acute and chronic CO inhalation (65). Brewer (69), using pentobarbital-treated dogs, also reported hypotension. Norman et al. (24) noted that aortic BP tended to fall as COHb increased from 0 to 70% in dogs. MacMillan (70) ventilated lightly anesthetized and paralyzed rats with 1% CO over 60 min in examining cerebral metabolic events. Mean arterial BP fell steeply at first and more gradually afterward.

In rats briefly exposed to 2000 and 4000 ppm CO, mean arterial BP fell at 40, 50, and 60% COHb (71). This involved decreases in both systolic and diastolic BP, but the latter was more pronounced, increasing pulse pressure. Kanten et al. (19) observed profound decreases in arterial BP, left ventricular systolic pressure, and total systemic peripheral resistance (TPR) in rats over 48 hr as COHb rose from 7% to 35–38%. In this study, BP also declined in rats IP injected with CO, where COHb reached 56% after 1 hr. Most recently, King and his colleagues (22,65) also observed large decreases in mean arterial BP and TPR in unconscious dogs at 50 to 65% COHb. However, they noted that

hindlimb blood flow remained unchanged although Q increased. Blood flow increased when the hindlimb was denervated. This suggests that Q is directed to non-muscle areas of the body in the presence of COHb and that intact sympathetic innervation is required to achieve this redistribution.

Conscious Animals. Hypotension has also been reported in rabbits inhaling 0.2% CO for less than 1 hr; arterial BP and TPR fell (31,32). In rabbits at 28% COHb, Kleinert et al. (72) also saw a decline in arterial BP. Using goats at 45 to 55% COHb, Santiago and Edelman (27) reported a decrease in diastolic arterial BP, but no consistent change in systolic BP.

Decreased BP was also noted in conscious rats whose COHb reached 65 to 70% after 80 min (33). This was correlated with impaired neurological function, such as decreased nerve conduction velocity. Okeda et al. (73) believe that the hypotension accompanying carboxyhemoglobinemia is the primary causative factor in CO-induced encephalopathy. Even in rabbits lacking hemoglobin, arterial BP fell markedly during inhalation of 5, 10, and 20% CO (37).

Traystman and Fitzgerald (74) found that cerebral vascular resistance decreased more with CO than with hypoxic hypoxia, since BP fell with the former, but increased with the latter. Following carotid chemoreceptor resection, BP also fell with hypoxic hypoxia. In another acute study, both mean arterial BP and TPR fell in anesthetized paralyzed dogs given CO over 15 to 20 min (21). The depressant effects of CO on these parameters was far greater than that of hypoxic hypoxia. As before, these differences were eliminated by resection of the carotid bodies, suggesting their role in the response to hypoxic hypoxia but not in that to CO hypoxia.

Many studies involving CO, however, report no change, or an increase, in BP. For example, Gutierrez et al. (23) failed to see changes in either mean systemic or mean pulmonary BPs in anesthetized dogs at 50% COHb, whether CO was administered by inhalation or by IP injection. In addition, neither systemic nor pulmonary vascular resistance changed significantly in that study. No significant change was found by Cramlet et al. (29) in left ventricular mean pressure in conscious dogs acutely attaining 10, 20, and 30% COHb. Neither Adams and his co-workers (28), examining left ventricular pressure in awake dogs at 5 to 20% COHb over 30 min, nor Lillelei and his collaborators (18), measuring arterial BP of dogs at 50% COHb over the same time period, saw changes.

Humans. Chiodi and co-workers (14) found that systolic BP rose or remained steady, while diastolic values fell in humans at COHb as high as 48%. The observations of others (75,76) also suggest decreased TPR in CO poisoning. Peripheral vasodilation and pooling of blood occurs in organs other than the skin in people working at 25 to 33% COHb (40). It is suggested that this contributes to slightly elevated core temperature in carboxyhemoglobinemia. Acute CO poisonings in humans is reported to be accompanied by lability of BP,

including peripheral vasodilation; long-term CO exposure often produces hypotension (41).

On the other hand, Stewart et al. (39) reported no change in systolic or diastolic blood pressure in men at 0 to 15% COHb. Even during exercise at 18 to 20% COHb, arterial BP in humans, as at rest, was not different from men in room air at the same activity level (43). However, since Q increased with higher work intensity in this study, calculated TPR decreased considerably.

Chronic

Penney et al. (20) reported a sharp decline in both systemic and pulmonary resistances in rats held at 38 to 42% COHb for 42 days. However, Lillehei et al. (18) reported normal BP in dogs gradually acclimatized to 1000 ppm CO for 6 to 8 hr per day for a year. Likewise, James et al. (52) saw no significant change in peak left ventricular pressure and TPR in conscious goats maintained at 20% COHb for 2 weeks. There was no change in BP in *Cynomolgus* monkeys after 8 months at 11.2% COHb (53).

While Klausen et al. (56) found no changes in systolic and diastolic BP in resting men maintained at 12% COHb for 8 days, the former pressure increased and the latter fell relative to working air controls when the men inhaling CO also worked.

Even at rest, increases in femoral artery pressure were seen in dogs inhaling CO (17), and the same occurred in systolic, diastolic, and mean arterial BP and right ventricular systolic pressure in anesthetized dogs at 26.5 and 41.6% COHb (16). Modest increases in left and right ventricular systolic pressure and mean aortic pressure have been reported in rats held at 38 to 42% COHb for 42 days (20). The BP of rabbits was reported to be higher following 100 ppm CO exposure for 2500 hr (55) and after inhalation of 1500 ppm CO for 3 hr each day for many weeks (77). In the latter case, the elevated BP failed to renormalize postexposure when CO treatment exceeded 7 weeks.

It is clear, that as with HR, SV, and Q , there is wide variability in the BP response to CO in different species and under various experimental conditions. Human studies have generally failed to demonstrate systemic hypotension with CO, while a number of animal studies have. This difference may be, as with the other hemodynamic parameters reviewed here, largely a function of the lower COHb levels used in human studies; however, failure to show profound systemic hypotension in man brings into question current explanations of CO encephalopathy.

Generally, a COHb saturation above 20% is accomplished by some fall in BP in most species. For example, in the recent study by Kantén et al. (19), mean arterial BP fell 37 mm Hg as COHb increased from 0 to 38%. At the same time, Q rose to 78% above controls mainly through increased SV. These investigators suggest that depressed afterload contributes to SV augmentation. They believe that hypotension results primarily from

the direct local effect of CO producing peripheral vascular dilation, as demonstrated by Coburn (60) in isolated aorta.

Lahiri (78) found that most carotid body receptors are not stimulated by moderate COHb saturation or hypotension. He interpreted this to mean that the receptor tissue is not sensitive to hemoglobin-bound oxygen; presumably, due to an exceedingly high blood flow rate. On the other hand, these manipulations stimulate aortic chemoreceptor activity, indicating hemoglobin-bound oxygen was a stimulus there. Blood flow to the aortic body is low and critical. A subsequent study confirmed this (79). Thus, the response to CO is different from that to other hypoxic stimuli. The usual mechanisms responsible for sensing hypoxia and initiating a response fail, due to the nature of CO-hemoglobin binding. The responses that occur are those slower reactions to local hypoxia and are not as effective as the rapid multiple responses triggered by hypoxic hypoxia.

Coronary and Cerebral Blood Flow

There is general agreement that vascular resistance falls and blood flow increases in the coronary circulation during carboxyhemoglobinemia. This presumably occurs because of the great sensitivity of the myocardium to hypoxemia, the depressed mixed venous P_{O_2} at the coronary sinus (17), decreased arteriovenous oxygen content difference across the coronary circulation, and the fall in myocardial oxygen consumption (17,28).

For example, Ayres et al. (17) reported increases in coronary blood flow in both humans and dogs over a wide range of COHb saturation. In the human studies, flow increased when COHb was raised to between 5 and 10%. Increased coronary blood flow also results from cigarette smoking in normal men (80), but this may not occur in men with coronary artery disease (81). Adams et al. (28), using conscious dogs, saw a 13% increase in coronary blood flow at 4% COHb, and a 54% increase at 20% COHb. They suggest a linear relationship exists between COHb and blood flow.

Young and Stone (30) found substantial increases in coronary blood flow and decreases in diastolic coronary resistance with no change in myocardial oxygen consumption in chronically instrumented, conscious dogs at 30% COHb. While this occurred in paced animals, indicating the flow increase was independent of HR, it was attenuated by blockage with propranolol and atropine. They suggest that coronary vasodilation observed with reduced arterial oxygen saturation is mediated through a neurogenic mechanism. Scharf et al. (82), on the other hand, used isolated perfused dog hearts to examine the effects of both CO and hypoxic hypoxia in decreasing coronary vascular resistance. At constant coronary flow with β -blockade, vascular resistance decreased more with CO than with hypoxic hypoxia.

More recently, McGrath and collaborators (83-85), using a bloodless, isolated perfused heart preparation, demonstrated that CO results in greater coronary vasodilation than nitrogen anoxia, strengthening the con-

tention that CO has a direct effect on vascular smooth muscle discrete from an anoxic one.

Not only does CO appear to increase coronary blood flow globally, it also increases the number of open capillary beds (72). The presence of CO, however, leaves the endocardium relatively under-perfused as compared to the epicardium (16).

Increased cerebral blood flow (CBF) was observed in anesthetized goats where COHb saturation increased to 65% in 10 min. The investigators (86) saw 133 and 200% increases in CBF in anesthetized dogs when COHb levels were raised to 30 and 51%, respectively. These CBF levels were significantly greater than those produced by cyanide. Koehler et al. (88,89) reported greater CBF in unanesthetized newborn lambs and in adult sheep exposed to CO hypoxia than in those exposed to hypoxic hypoxia; suggesting this be a function of the leftward shift of the oxyhemoglobin dissociation curve that accompanies COHb. Their findings are consistent with the results of Traystman and Fitzgerald (74) of a greater decrease in cerebral vascular resistance with CO.

Myocardial Contractility

The first derivative of changing ventricular pressure (dP/dt) has been used by many investigators as one index of contractility. Adams et al. (28) reported no change in maximum dP/dt in conscious dogs at 5 to 20% COHb. However, using isolated perfused dog hearts treated with CO, Schaf and co-workers (82) saw increases in dP/dt that were eliminated with β -adrenergic blocking agents. In support of this, Cramlet et al. (29) observed increases to dP/dt_{\max} relative to air controls in conscious dogs reaching 10 to 30% COHb. Penney et al. (20), working with rats maintained at 40% COHb for 42 days, also reported elevated left ventricular dP/dt_{\max} during the first 2 weeks relative to controls. Nevertheless, it is unclear to what extent increased dP/dt is simply the result of increased HR versus that resulting from enhanced sympathetic drive and circulating catecholamines.

Right ventricle and left ventricle dP/dt_{\max} rose 58% and 41% above controls, respectively, in dogs acutely inhaling smoke from burning charcoal and sawdust (26). COHb reached 72%, while P_{O_2} fell and P_{CO_2} rose in that study.

Stewart and his group (39), on the other hand, noted no change in myocardial contractility as judged by pre-ejection time in humans at 0 to 15% COHb, and James et al. (52) drew the same conclusion for the left ventricle of conscious goats during 2 weeks at 20% COHb, based on estimates of V_{\max} . Recently, left ventricle dP/dt_{\max} has been reported to be unchanged in anesthetized rats at COHb of 7% to 35-38% over 48 hr (19). Ingenito et al. (90) suggested that CO may exert a direct negative inotropic effect on the myocardium.

Heart Work

Few data exist on myocardial work during carboxyhemoglobinemia. In pentobarbital anesthetized rats

maintained at 38 to 42% COHb for 6 weeks, mean stroke power in the presence of polycythemia was almost half that of controls (20). However, in a more recent study using normocythemic rats anesthetized with chloralose-urethan, stroke work and stroke power were unchanged over 48 hr at 7 to 38% COHb (19). In the latter case, even though SV and HR rose, arterial BP, a major contributor to work and power, fell.

Blood Volume

Total blood volume (BV) increases as another response to chronic CO exposure, and serves to increase cardiac preload. For example, Wilks and colleagues (91) found a 52% increase in BV in dogs exposed to 800 to 1000 ppm CO for 6 to 8 hr daily for 20 weeks, while plasma volume increased only 17%. Hence, most of the volume increase was due to greater erythrocyte mass. Zebro et al. (92) also reported a very large BV increase in mice maintained at 74% COHb for more than two-thirds of a 36-day CO exposure period; however, they measured BV merely by draining the blood from sacrificed animals. Theodore and collaborators (49), in a very long-term study, found a 39% BV increase in monkeys and a 31% increase in dogs exposed to 355 ppm CO for 71 days, followed by 444 ppm CO for an additional 97 days. In the monkeys, this involved a 145% increase in erythrocyte volume and a 6% decrease in plasma volume. In the dogs, red cell volume increased 69%, while plasma volume increased 19%.

BV increases within a few days in adult rats inhaling 500 ppm CO, reaching a value about 60% above controls after 42 days (Penney and Davidson, unpublished data). This results from an increase in erythrocyte mass, with no change or a slight fall in plasma volume, as in hypoxic hypoxia (93). In rats exposed to incrementally increasing CO concentrations (i.e., 250, 500, 750, and 1300 ppm), blood volume increases in a nearly linear fashion, more than doubling at the highest CO level as the result of a more than threefold increase in erythrocyte volume. Real hematocrit (no trapped plasma) rises from 49 to 74% (Penney et al., unpublished data).

In contrast, Ogawa et al. (94), in a short-term study, noted that BV fell 20% after 30 min at 60% COHb, mainly due to a sharp reduction in plasma volume caused by increased vascular permeability. This led to a 20% rise in hematocrit. However, at a lower COHb (29%) level, Syvertsen and Harris (95) saw no change in hematocrit until 72 hr after starting in dogs inhaling 195 ppm CO, in contrast to hypoxic hypoxia where hematocrit rose almost immediately, suggesting the absence of splenic contraction in CO hypoxia. Siggard-Anderson et al. (96) found only slight or no change in plasma volume in human subjects after 12 hr and 8 days exposure to CO.

Conclusions

We might summarize the time-course of the response to CO by drawing together the findings from one model

system with which considerable work has been done—the rat (Fig. 1). Although much of the data have been gathered under anesthesia, conscious data, where obtainable, are confirmatory. Unfortunately, no other comprehensive acute and long-term studies of CO poisoning have been carried out by a single laboratory with another species (e.g., dogs, in which the bulk of CO work has been done). Presumably, the picture presented here is a fairly general one.

CO is taken up rapidly to an equilibrium blood saturation (11,12). Increase in Q as the result of increases in SV and HR occur early (e.g., minutes), at COHb saturations of 10% or less (19). At the same time, arterial BP and TPR are sharply depressed (70). Within 3 to 5 days, developing polycythemia is detectable (50,51), at least at CO levels above a threshold value of 100 ppm (97), resulting in a gradually increasing BV. While this improves oxygen-carrying capacity, tissue oxygen delivery may remain impaired because CO increases hemoglobin-oxygen affinity (98). Nonetheless, elevated SV, HR, and Q subside, as a smaller contribution by the latter to oxygen transport is required in the presence of polycythemia. At the same time, however, increased blood viscosity, previously normal during initial carboxyhemoglobinemia, contributes to raising stroke and minute work, especially at CO concentrations of 500 ppm and above, which greatly elevate hematocrit. Increased viscosity acts in part to return BP and TPR toward, but not to, normal. The lung vasculature, in fact, is very sensitive to increased blood viscosity (93) and flow (99), probably resulting in some degree of pulmonary hypertension.

Cardiomegaly (i.e., cardiac hypertrophy), although not in the mainstream of this review, is part and parcel of the chronic response to CO, and surely modifies the heart's subsequent hemodynamic response to CO. It develops in both ventricles and atria with the addition of new myocardial constituents (97) and involves primarily an increase in lumen dimensions with some small increase in wall thickness of the ventricles (i.e., eccentric hypertrophy) (100). While CO-induced cardiomegaly is probably mainly a product of increased preload (e.g., increased venous return, BV), enhanced sympathetic drive and possibly viscosity- and flow-induced elevated afterload may have roles. Surely, a subtle interplay exists between the hemodynamic responses to CO which occur early, and the secondary acclimative responses (e.g., polycythemia, increased BV, cardiomegaly), such that adequate tissue oxygenation is sustained, or at a minimum, improved over that in their absence.

After 5 to 6 weeks of CO exposure, Q, SV, and HR continue somewhat supranormal. Arterial BP and TPR remain depressed, while stroke work and minute work (i.e., power) are elevated. Rapid elimination of CO, effected by breathing room air, results in a number of charges which persist for several weeks: TPR and BP are elevated 52 and 40%, respectively, presumably because of high blood viscosity in the absence of peripheral vasodilation. While Q returns to normal, SV is de-

pressed, probably as the result of the increased afterload. Tachycardia continues, providing normal output, while stroke work and minute work rise to still higher levels than earlier. The latter illustrates the importance of vasodilation during chronic carboxyhemoglobinemia, maintaining heart work at a far lower level than would otherwise be the case with polycythemia present. The polycythemia and cardiomegaly then gradually subside over the following 20 to 30 days (51,101).

REFERENCES

- Morandi, M., and Eisenbud, M. Carbon monoxide exposure in New York City: A historical review. *Bull. N. Y. Acad. Med.* 56: 817-828 (1980).
- Bernard, C. *Lecons sur les effets des substances toxiques et medicamenteuses*. Bailliere, Paris, 1857.
- Haldane, J. S. The action of carbonic oxide on man. *J. Physiol.* 18: 402-462 (1895).
- Pankow, D. *Toxikologie des Kohlenmonoxids*. Veb Verlag Volk Und Gesundheit, Berlin, 1981.
- Ginsberg, M. D. Carbon monoxide. In: *Experimental and Clinical Neurotoxicology* (P. S. Spencer and H. H. Schaumburg, Eds.), Williams and Wilkins, Baltimore, MD, 1980, pp. 374-394.
- Turino, G. M. Effect of carbon monoxide on the cardiovascular system: Carbon monoxide toxicity: Physiology and biochemistry. In: *Impact of the Environment on Cardiovascular Disease*. American Heart Association, 1980, pp. 253A-259A.
- McGrath, J. J. Physiological effects of carbon monoxide. In: *Air Pollution*. Academic Press, New York, 1982, pp. 147-181.
- Forbes, W. H., Sargent, F., and Roughton, F. J. W. The rate of carbon monoxide uptake by normal men. *Am. J. Physiol.* 143: 594-608 (1945).
- Peterson, J. E., and Stewart, R. D. Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. *J. Appl. Physiol.* 39: 633-638 (1975).
- Joumard, R., Chiron, M., Vidon, R., Maurin, M., and Rouzioux, J.-M. Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. *Environ. Health Perspect.* 41: 277-289 (1981).
- Tyuma, I., Ueda, Y., Imaizumi, K., and Kosaka, H. Prediction of the carbon-monooxyhemoglobin levels during and after carbon monoxide exposures in various animal species. *Jpn. J. Physiol.* 31: 131-143 (1981).
- Montgomery, M. R., and Rubin, R. J. The effect of carbon monoxide inhalation on *in vivo* drug metabolism in the rat. *J. Pharmacol. Exper. Ther.* 179: 465-473 (1971).
- Haggard, H. W. Studies in carbon monoxide asphyxia. I. The behavior of the heart. *Am. J. Physiol.* 56: 390-403 (1921).
- Chiodi, H., Dill, D. B., Consolazio, F., and Horvath, S. M. Respiratory and circulatory responses to acute CO poisoning. *Am. J. Physiol.* 134: 683-693 (1941).
- Killick, E. M. The acclimatization of the human subject to atmospheres containing low concentrations of carbon monoxide. *J. Physiol.* 87: 41-55 (1936).
- Einzig, S., Nicoloff, D. M., and Lucas, R. V. Jr. Myocardial perfusion abnormalities in carbon monoxide poisoned dogs. *Can. J. Physiol. Pharmacol.* 58: 396-405 (1980).
- Ayres, S. M., Giannelli, S., Jr., and Mueller, H. Myocardial and systemic responses to carboxyhemoglobin. *Ann. N. Y. Acad. Sci.* 174: 268-293 (1970).
- Lillehei, J. P., Wilks, S. S., and Carter, E. T. Circulatory responses of normal and of CO-acclimatized dogs during CO inhalation. *Fed. Proc.* 13: 89 (abstr.) (1954).
- Kanten, W. E., Penney, D. G., Francisco, K., and Thill, J. E. Hemodynamic responses to acute carboxyhemoglobinemia in the rat. *Am. J. Physiol.* 244: H320-H327 (1983).
- Penney, D. G., Sodd, P. C., and Cutilletta, A. Cardiodynamic changes during prolonged carbon monoxide exposure in the rat. *Toxicol. Appl. Pharmacol.* 50: 213-218 (1979).
- Sylvester, J. T., Scharf, S. M., Gilbert, R. D., Fitzgerald, R. S., and Traystman, R. J. Hypoxic and CO hypoxia in dogs: Hemodynamics, carotid reflexes, and catecholamines. *Am. J. Physiol.* 236: H22-H28 (1979).
- King, C. E., Cain, S. M., and Chapler, C. K. Whole body and hindlimb cardiovascular responses of the anesthetized dog during CO hypoxia. *Can. J. Physiol. Pharmacol.* 62: 769-774 (1984).
- Gutierrez, G., Rotman, H. H., Reid, C. M., and Dantzker, D. R. Comparison of canine cardiovascular response to inhaled and intraperitoneally infused CO. *J. Appl. Physiol.* 58: 558-563 (1985).
- Norman, J. N., Douglas, T. A., and Smith, G. Respiratory and metabolic changes during carbon monoxide poisoning. *J. Appl. Physiol.* 21: 848-852 (1966).
- Dergal, E., Hodjati, H., Goldbaum, L., and Absolon, K. Effects of cardiac pacing in acute carbon monoxide intoxication in dogs. *Chest* 70: 424 (Abstr.) (1976).
- Pindok, M. T., Dunn, R. B., Nuzzarello, J., and Glaviano, V. V. Cardiovascular responses of the dog to acute smoke toxicity. *Circ. Shock* 11: 35-44 (1983).
- Santiago, T. V., and Edelman, N. H. Mechanism of the ventilatory response to carbon monoxide. *J. Clin. Invest.* 57: 977-986 (1976).
- Adams, J. D., Erickson, H. H., and Stone, H. L. Myocardial metabolism during exposure to carbon monoxide in the conscious dog. *J. Appl. Physiol.* 34: 238-242 (1973).
- Cramlet, S. H., Erickson, H. H., and Gorman, H. A. Ventricular function following acute carbon monoxide exposure. *J. Appl. Physiol.* 39: 482-486 (1975).
- Young, S. H., and Stone, H. L. Effect of a reduction in arterial oxygen content (carbon monoxide) on coronary flow. *Aviat. Space Environ. Med.* 47: 142-146 (1976).
- Korner, P. I. The role of the arterial chemoreceptors and baroreceptors in the circulatory response to hypoxia of the rabbit. *J. Physiol.* 180: 279-303 (1965).
- Korner, P. I. Operation of the central nervous system in reflex circulatory control. *Fed. Proc.* 39: 2504-2512 (1980).
- Petajan, J. H., Packham, S. C., Frens, D. B., and Dinger, B. G. Sequelae of carbon monoxide-induced hypoxia in the rat. *Arch. Neurol.* 33: 152-157 (1976).
- Ayres, S. M., Mueller, H. S., Gregory, J. J., Giannelli, S., Jr., and Penny, J. L. Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHb). *Arch. Environ. Health* 18: 699-709 (1969).
- Fukuda, T., and Kobayashi, T. On the relation of chemoreceptor stimulation to epinephrine secretion in anoxemia. *Jpn. J. Physiol.* 11: 467-475 (1961).
- Pankow, D., and Ponsold, W. Effect of single and repeated carbon monoxide intoxications on urinary catecholamine excretion in rats. *Acta Biol. Germ.* 37: 1589-1593 (1978).
- Takano, T., Miyazaki, Y., Shimoyama, H., Maeda, H., Okeda, R., and Funata, N. Direct effects of carbon monoxide on cardiac function. *Int. Arch. Occup. Environ. Health* 49: 35-40 (1981).
- Cosby, R. S., and Bergeron, M. Electrocardiographic changes in carbon monoxide poisoning. *Am. J. Cardiol.* 11: 93-96 (1963).
- Stewart, R. D., Peterson, J. E., Fisher, T. N., Hosko, M. J., Baretta, E. D., Dodd, H. C., and Herrmann, A. A. Experimental human exposure to high concentrations of carbon monoxide. *Arch. Environ. Health* 26: 1-7 (1973).
- Nielson, B. Thermoregulation during work in carbon monoxide poisoning. *Acta Physiol. Scand.* 82: 98-106 (1971).
- Lazarev, N. V. Carbon monoxide. In: *Toxic Substances in Industry*, Vol. 2 (N. V. Lazarev, Ed.), Khimiya, Moscow, 1965, pp. 198-218 (in Russian).
- Shepherd, R. J. The influence of small doses of carbon monoxide upon heart rate. *Respiration* 29: 516-521 (1972).
- Vogel, J. A., and Gleser, M. A. Effect of carbon monoxide on oxygen transport during exercise. *J. Appl. Physiol.* 32: 234-239 (1972).
- Vogel, J. A., Gleser, M. A., Wheeler, R. C., and Whitten, B. K. Carbon monoxide and physical work capacity. *Arch. Environ. Health* 24: 198-203 (1972).
- Pirnay, F., Dujardin, J., Deroanne, R., and Petit, J. M. Mus-

- cular exercise during intoxication by carbon monoxide. *J. Appl. Physiol.* 31: 573-575 (1971).
46. Gliner, J. A., Raven, P. B., Horvath, S. M., Drinkwater, B. L., and Sutton, J. C. Man's physiologic response to longterm work during thermal and pollutant stress. *J. Appl. Physiol.* 39: 628-632 (1975).
 47. Chevalier, R. B., Krumholz, R. A., and Ross, J. C. Reaction of non-smokers to carbon monoxide inhalation. *JAMA* 198: 1061-1064 (1966).
 48. Asmussen, E., and Vinther-Paulsen, N. On the circulatory adaptations to arterial hypoxemia (CO-poisoning). *Acta Physiol. Scand.* 19: 115-124 (1949).
 49. Theodore, J., O'Donnell, R. D., and Back, K. C. Toxicological evaluation of carbon monoxide in humans and other mammalian species. *J. Occup. Med.* 13: 242-255 (1971).
 50. Penney, D. G., Dunham, E., and Benjamin, M. Chronic carbon monoxide exposure: Time course of hemoglobin, heart weight and lactate dehydrogenase isozyme changes. *Toxicol. Appl. Pharmacol.* 28: 493-497 (1974).
 51. Penney, D. G., and Bishop, P. A. Hematologic changes in the rat during and after exposure to carbon monoxide. *J. Environ. Pathol. Toxicol.* 2: 407-415 (1978).
 52. James, W. E., Tucker, C. E., and Grover, R. F. Cardiac function in goats exposed to carbon monoxide. *J. Appl. Physiol.* 47: 429-434 (1979).
 53. Dhindsa, D. S., and Ochsner, A. J. III. Hemodynamic and metabolic effects of chronic carbon monoxide exposure in Cynomolgus monkeys (*Macaca fasciculatus*). *J. Med. Primatol.* 10: 255-262 (1981).
 54. Stupfel, M., and Bouley, G. Physiological and biochemical effects on rats and mice exposed to small concentrations of carbon monoxide for long periods. *Ann. N.Y. Acad. Sci.* 174: 342-368 (1970).
 55. Truhaut, R., Baudene, C., Claude, J. R., and Jacotot, B. Studies on the effects of prolonged exposure of rabbits and rats to weak concentrations of carbon monoxide. III. Effects on the cardiovascular system. *Arch. Mal. Prof. Med. Trav. Secur. Soc.* 29: 189-196 (1968).
 56. Klausen, K., Rasmussen, B., Gjellerod, H., Madsen, H., and Peterson, E. A comparison of prolonged exposure to carbon monoxide and hypoxia in man. *Scand. J. Clin. Lab. Invest.* 22 (Suppl. 103): 26-38 (1968).
 57. Drabkin, D. L., Lewey, F. H., Bellet, S., and Ehrlich, W. H. The effect of replacement of normal blood by erythrocytes saturated with carbon monoxide. *Am. J. Med. Sci.* 205: 755-756 (1943).
 58. Ramirez, R. G., Albert, S. N., Agostini, J. C., Basu, A. P., Goldbaum, L. R., and Absolon, K. B. Lack of toxicity of transfused carboxyhemoglobin red blood cells and carbon monoxide inhalation. *Surg. Forum* 25: 165-168 (1974).
 59. Goldbaum, L. R., Ramirez, R. G., and Absolon, K. B. Joint committee on Aviation Pathology: XIII. What is the mechanism of carbon monoxide toxicity? *Aviat. Space Environ. Med.* 46: 1289-1291 (1975).
 60. Coburn, R. F. Mechanisms of carbon monoxide toxicity. *Prev. Med.* 8: 310-322 (1979).
 61. Orellano, T., Dergal, E., Alijani, M., Briggs, C., Vasquez, J., Goldbaum, L., and Absolon, K. B. Studies on the mechanism of carbon monoxide toxicity. *J. Surg. Res.* 20: 485-487 (1976).
 62. Chen, K. C., McGrath, J. J., and Vostal, J. J. Effects of intraperitoneal injection of carbon monoxide on heart and respiration. *Fed. Proc.* 40: 609 (Abstr.) (1981).
 63. Wilks, S. S. Effects of pure carbon monoxide gas injection into the peritoneal cavity of dogs. *J. Appl. Physiol.* 14: 311-312 (1959).
 64. Halebian, P., Robinson, N., and Barie, P. Whole body oxygen utilization during carbon monoxide poisoning and isocapnic hypoxia. *J. Trauma* 26: 110-117 (1986).
 65. Killick, E. M. Carbon monoxide anoxemia. *Physiol. Rev.* 20: 313-344 (1940).
 66. King, C. E., Cain, S. M., and Chapler, C. K. The role of aortic chemoreceptors during severe CO hypoxia. *Can. J. Physiol. Pharmacol.* 63: 509-514 (1985).
 67. Asmussen, E., and Chiodi, H. The effect of hypoxemia on ventilation and circulation in man. *Am. J. Physiol.* 132: 426-436 (1941).
 68. Ayres, S. M., Giannelli, S., Jr., and Armstrong, R. G. Carboxyhemoglobin: Hemodynamic and respiratory responses to small concentrations. *Science* 149: 193-194 (1965).
 69. Brewer, N. R. Blood-pressure responses to acute carbon monoxide poisoning. *Am. J. Physiol.* 120: 91-99 (1937).
 70. MacMillan, V. Cerebral carbohydrate metabolism during acute carbon monoxide intoxication. *Brain Res.* 121: 271-286 (1977).
 71. Silbaugh, S. A., and Horvath, S. M. Effect of acute carbon monoxide exposure on cardiopulmonary function of the awake rat. *Toxicol. Appl. Pharmacol.* 66: 376-382 (1982).
 72. Kleinert, H. D., Scales, J. L., and Weiss, H. R. Effects of carbon monoxide or low oxygen gas mixture inhalation on regional oxygenation, blood flow, and small vessel blood content of the rabbit heart. *Pflugers Arch.* 383: 105-111 (1980).
 73. Okeda, R., Funata, N., Takano, T., Miyazaki, Y., Higashino, F., Yokoyama, K., and Manabe, M. The pathogenesis of carbon monoxide encephalopathy in the acute phase: Physiological and morphological correlation. *Acta Neuropathol.* 54: 1-10 (1981).
 74. Traystman, R. J., and Fitzgerald, R. S. Cerebral circulatory responses to hypoxic hypoxia and carbon monoxide hypoxia in carotid baroreceptor and chemoreceptor denervated dogs. *Acta Neurol. Scand.* 56 (Suppl. 64): 294-295 (1977).
 75. Asmussen, E., and Erreboe-Knudsen, E. O. Studies in acute but moderate CO-poisoning. *Acta Physiol. Scand.* 6: 67-78 (1943).
 76. Pauli, H. G., Truniger, B., Larsen, J. K., and Mulhausen, R. O. Renal function during prolonged exposure to hypoxia and carbon monoxide. I. Glomerular filtration and plasma flow. *Scand. J. Clin. Lab. Invest.* 22 (Suppl. 103): 55-60 (1968).
 77. Kubota, M. The behavior of blood pressure in chronic carbon monoxide poisoning. *Med. J. Shinshu Univ.* 4: 53-64 (1959).
 78. Lahiri, S. Role of arterial oxygen flow in peripheral chemoreceptor excitation. *Fed. Proc.* 39: 2648-2652 (1980).
 79. Lahiri, S., Mulligan, E., Nishino, T., Modashi, A., and Davies, R. O. Relative responses of aortic body chemoreceptors to carboxyhemoglobinemia. *J. Appl. Physiol.* 50: 580-586 (1981).
 80. Barger, L. M. Jr., Ehmke, D., Gonlubol, F., Castellanos, A., Siegel, A., and Bing, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. *Circulation* 15: 251-257 (1957).
 81. Regan, T. J., Hellems, H. K., and Bing, R. J. Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease. *Ann. N. Y. Acad. Sci.* 90: 186-189 (1960).
 82. Scharf, S. M., Permutt, S., and Bromberger-Barnea, B. Effect of hypoxic and CO hypoxia on isolated hearts. *J. Appl. Physiol.* 39: 752-768 (1975).
 83. McGrath, J. J. The effects of carbon monoxide on the heart: An in vitro study. *Pharmacol. Biochem. Behav.* 21: 99-102 (1984).
 84. McGrath, J. J., and Smith, D. L. Response of rat coronary circulation to carbon monoxide and nitrogen hypoxia. *Proc. Soc. Exp. Biol. Med.* 177: 132-136 (1984).
 85. Chen, K. C., and McGrath, J. J. Response of the isolated heart to carbon monoxide and nitrogen anoxia. *Toxicol. Appl. Pharmacol.* 81: 363-370 (1985).
 86. Doblar, D. D., Santiago, T. V., and Edelman, N. H. Correlation between ventilatory and cerebrovascular responses to inhalation of CO. *J. Appl. Physiol.* 43: 455-462 (1977).
 87. Pitt, B. R., Radford, E. P., Gurtner, G. H., and Traystman, R. J. Interaction of carbon monoxide and cyanide on cerebral circulation and metabolism. *Arch. Environ. Health* 34: 354-359 (1979).
 88. Koehler, R. C., Jones, M. D., Jr., and Traystman, R. J. Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. *Am. J. Physiol.* 243: H27-H32 (1982).
 89. Koehler, R. C., Traystman, R. J., Zeger, S., Rogers, M. C., and Douglas Jones, M., Jr. Comparison of cerebrovascular response to hypoxic and carbon monoxide hypoxia in newborn and adult sheep. *J. Cereb. Blood Flow Metab.* 4: 115-122 (1984).
 90. Ingenito, A. J., Fiedler, P. C., and Procita, L. Negative inotropic action of carbon monoxide on the isolated isovolumic heart

- with a hemoglobin-free perfusate. *Fed. Proc.* 33: 503 (Abstr.) (1974).
91. Wilks, S. S., Tomashefski, J. F., and Clark, R. T., Jr. Physiological effects of chronic exposure to carbon monoxide. *J. Appl. Physiol.* 14: 305-310 (1959).
 92. Zebro, T., Littleton, R. J., and Wright, E. A. Adaptation of mice to carbon monoxide and the effect of splenectomy. *Virchows Arch. A Pathol. Anat. Histol.* 371: 35-51 (1976).
 93. Ostadal, B., Ressler, J., Urbanova, D., Widemsky, J., Prochazka, J., Kasalicky, J., and Pelouch, V. The role of polycythemia in the development of experimental high altitude hypertension and right ventricular hypertrophy. *Prog. Resp. Res.* 9: 130-137 (1975).
 94. Ogawa, M., Shimazaki, S., Tanaka, N., Ukai, T., and Sugimoto, T. Blood volume changes in experimental carbon monoxide poisoning. *Ind. Health* 12: 121-125 (1974).
 95. Syvertsen, G. R., and Harris, J. A. Erythropoietin production in dogs exposed to high altitude and carbon monoxide. *Am. J. Physiol.* 225: 293-299 (1973).
 96. Siggard-Anderson, J., Petersen, F. B., Hansen, T. I., and Mellemgaard, K. Plasma volume and vascular permeability during hypoxia and carbon monoxide exposure. *Scand. J. Clin. Lab. Invest.* 22 (Suppl. 103): 39-48 (1968).
 97. Penney, D. G., Benjamin, M., and Dunham, E. Effect of carbon monoxide on cardiac weight as compared with altitude effects. *J. Appl. Physiol.* 37: 80-84 (1974).
 98. Penney, D., and Thomas, M. Hematological alterations and response to acute hypobaric stress. *J. Appl. Physiol.* 39: 1034-1037 (1975).
 99. Rabinovitch, M., Konstam, M. A., Gamble, W. J., Papanicolaou, N., Aronovitz, M. J., Treves, S., and Reid, L. Changes in pulmonary blood flow affect vascular response to chronic hypoxia in rats. *Circ. Res.* 52: 432-441 (1983).
 100. Penney, D. G., Barthel, B. G., and Skoney, J. A. Cardiac compliance and dimensions in carbon monoxide-induced cardiomegaly. *Cardiovasc. Res.* 18: 270-276 (1984).
 101. Styka, P. E., and Penney, D. G. Regression of carbon monoxide-induced cardiomegaly. *Am. J. Physiol.* 235: H516-H522 (1978).